Restoring Invisible and Abandoned Trials

The RIAT concept

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BMJ
University of Maryland
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Disclosure Statement

• I have a UK National Institute for Health Research grant to carry out a Cochrane review of neuraminidase inhibitors (www.hta.ac.uk/2352).

• I received €1500 from the European Respiratory Society in support of my travel to the society’s September 2012 annual congress in Vienna, where I gave an invited talk on oseltamivir.
Access to Clinical Trial Data
“Patients, researchers, pharmacists, doctors and regulators everywhere will benefit from publication of clinical trial results.”
“encourage unbiased publication of clinical trial results in the future by treating deliberate reporting biases as a form of research misconduct.”
“Why aren’t all clinical trial data routinely available for independent scrutiny once a regulatory decision has been made?”

How have commercial companies been allowed to evaluate their own products and then to keep large and unknown amounts of the data secret even from the regulators?”

“Individual patient data from all trials of drugs should be readily available for scientific scrutiny.”

Quotes of Fiona Godlee, Editor-in-chief, BMJ

BMJ 2012;345:e7304
BMJ 2009;339:b5405
“Data sharing within each sector and across sectors could facilitate scientific and public health advances and could enhance analysis of safety and efficacy.”

Source: http://www.iom.edu/Activities/Research/SharingClinicalResearchData/2012-OCT-04.aspx
PhRMA and EFPIA

• “… we encourage all medical researchers … to promote medical and scientific advancement by … Enhancing Data Sharing with Researchers
• “Biopharmaceutical companies commit to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data …”

Source:
http://phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf
“We are taking this step because it is the right thing to do, both scientifically and for society”
“At Roche, we agree that high quality analysis of clinical trial data by scientific researchers can broaden knowledge about our medicines and benefit patients and public health.”

Roche Global Policy on Sharing of Clinical Trials Data

Clinical trials are critical for determining the safety and efficacy of new medicines and are integral to Roche’s strategy of developing innovative treatments that address the unmet medical needs of patients. Roche is committed to sharing clinical trial outcomes and has registered and posted summary reports for clinical trials on ClinicalTrials.gov and Roche-Trials.com since 2005. Alongside this posting, we actively seek presentation and publication of our clinical trial data at scientific congresses and in peer-reviewed journals.

Roche announced a new policy regarding clinical trial information sharing in February 2013 to provide even broader access to clinical trial information. Under the new policy we are providing access to clinical study reports (CSRs) on request. After 1 January 2014, researchers will also receive access to patient level data from our clinical trials after their requests have been reviewed by an independent panel of experts. Access will be given by the independent panel on the basis of good scientific merit. Patient-level data will be anonymised to respect the privacy of patients participating in our trials, in line with relevant laws and regulations.
“Pfizer believes that giving qualified scientific researchers access to patient-level data collected in clinical trials provides additional opportunities to conduct research that can improve patient care and help advance medical science.”
“Access to CT data in an analysable format will benefit public health in future.”

“The Agency respects and will not divulge commercially confidential data or information. In general, however, CT data cannot be considered CCI; the interests of public health outweigh considerations of CCI.”

Full Disclosure Needed for Clinical Drug Data

By THE EDITORIAL BOARD
Published: July 4, 2013

Pharmaceutical companies are under increasing pressure to release previously hidden data on how well their drugs work. The primary push for much greater transparency has come from the Cochrane Collaboration, an international network of experts based in Oxford, England; The British Medical Journal; and the European Medicines Agency, which recently proposed that, starting next year, clinical trial data be released once a drug is approved for marketing.

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The saga of Tamiflu, an anti-flu drug produced by Roche, a multinational company based in Switzerland, exemplifies the difficulties of extracting information vital to public health. In mid-2009 a Cochrane researcher was hired by the British and Australian governments to update his previous evaluation of Tamiflu, which had concluded that it reduced the risk of complications from the flu. The information was important because the drug was being stockpiled by the United States and other governments in the belief that it would help people survive a potentially severe epidemic of swine flu.

As described by Katie Thomas in The Times, eight of 10 studies that supposedly attested to its effectiveness had never been published. In December 2009, after failing to
Underreporting Research Is Scientific Misconduct

Iain Chalmers, FRCOG

Substantial numbers of clinical trials are never reported in print, and among those that are, many are not reported in such a way as to make the validity of their results questionable. A well-designed clinical trial is a form of research that is intended to provide information that will help in making decisions about patient care. However, the results of clinical trials are often not reported in sufficient detail to allow others to assess the validity of the findings. This can have important implications for the conduct of future research, as well as for the practice of medicine. The failure to report the results of clinical trials can lead to a loss of confidence in the research process, and can undermine the ability of researchers to conduct high-quality research.

Factors Influencing Publication of Research Results

Follow-up of Applications Submitted to Two Institutional Review Boards

Kay Dickersin, PhD; Yuan-I Min, MPH, MHS; Curtis L Meinert, PhD

Objective.—To investigate factors associated with the publication of research findings, in particular, the association between “significant” results and publication.

Design.—Follow-up study.

The JOURNAL have shown that a ten-year period...

JAMA. 1990;263(10):1405-1408

Fundamentally, today’s calls for clinical trial data are a response to two basic problems of *representation:*

1. **No representation**, i.e. invisibility (unpublished trials)

2. **Distorted representation** (misreported trials that go uncorrected)
“Data” means all the results and outcome measurements obtained from a Clinical Study. This includes a description and the results of any planned statistical analysis of the Data, as well as a listing of the most common Minor Adverse Events and a more detailed listing of Serious Adverse Events.
Abandoned trials – invisibility

“An additional analysis of published versus both published and unpublished evidence shows that published evidence overestimates the benefit of reboxetine, while underestimating harm.” BMJ 2010;341:c4942
Abandoned trials – invisibility

HHS 2005: “Critical assumptions. … Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality.” (p.D-20)

Abandoned trials – invisibility

Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations

Laurent Kaiser, MD; Cynthia Wat, MBBS, MRCP; Tracy Mills, MSc; Paul Maloney, MSc; Penelope Ward, MBBS; Frederick Hayden, MD

**Background:** Influenza causes lower respiratory tract complications (LRTCs), particularly bronchitis and pneumonia, in both otherwise healthy adults and those with underlying conditions. The aim of this study was to assess the effect of oseltamivir treatment on the incidence of LRTCs leading to antibiotic treatment and hospitalizations following influenza illness.

**Methods:** We analyzed prospectively collected data on LRTCs and antibiotic use from 356 subjects (age range, 13-97 years) with influenza-like illness enrolled in 10 placebo-controlled, double-blind trials of oseltamivir treatment.

**Results:** In adults and adolescents with a proven influenza illness, oseltamivir treatment reduced overall antibiotic use for any reason by 26.7% (14.9% vs 19.1% with placebo; P< .001) and the incidence of influenza-related LRTCs resulting in antibiotic therapy by 55% (4.6% vs 10.3% with placebo; P<.001). In those subjects considered at increased risk of complications, 74 (18.5%) of 401 placebo recipients developed an LRTC leading to antibiotic use compared with 45 (12.2%) of 368 oseltamivir recipients (34.0% reduction; P=.02). Hospitalization for any cause occurred in 18 (1.7%) of 1063 placebo recipients compared with 9 (0.7%) of 1350 oseltamivir-treated patients (93% reduction; P=.02). In contrast, among subjects with an influenza-like illness but without a confirmed influenza infection, the incidence of LRTCs (6.7% vs 5.3%), overall antibiotic use (19.7% vs 19.3%), or hospitalizations (1.7% vs 1.9%) was similar between placebo and oseltamivir recipients, respectively.

**Conclusion:** Oseltamivir treatment of influenza illness reduces LRTCs, antibiotic use, and hospitalization in both healthy and “at-risk” adults.

*Arch Intern Med. 2003;163:1667-1672*

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- Pooled analysis of 10 Roche funded RCTs from the late 1990s
  - 2/10 published (1397 patients)
  - 8/10 never published (2691 patients)
- Roche authored paper

“Conclusion: Oseltamivir treatment of influenza illness reduces LRTCs, antibiotic use, and hospitalization in both healthy and “at-risk” adults.”
“I did not perform an independent analysis of the primary data, which was not required or requested by *JAMA at the time of submission*, and *I do not have access to the primary data*, which I also never requested.”

“When asked a similar question, *Nicholson said he did not recall seeing the primary data*. He said that the *statistical analysis had been conducted by Roche* and he analysed the summary data”.

“As described on the FDA Web site, the published CLASS trial differs from the original protocol in primary outcomes, statistical analysis, trial duration, and conclusions. In particular, the unpublished data show that by week 65, celecoxib was associated with a similar number of ulcer complications as diclofenac and ibuprofen.”

GSK Paroxetine (Paxil) Study 329
• Original trial protocol specified 2 primary, 6 secondary outcomes
• All showed no difference between paroxetine and placebo
• Study published in *Journal of the American Academy of Child and Adolescent Psychiatry*
• Keller et al. paper: “paroxetine is generally well tolerated and effective for major depression in adolescents”
• Tamiflu trials: still unpublished
• CLASS study: no erratum, no retraction
• VIGOR study: no erratum, no retraction
• Study 329: no erratum, no retraction

… DESPITE DATA AVAILABILITY.
EDITORIAL

Clinical trial data: get them while you can

BMJ 2014; 348 doi: http://dx.doi.org/10.1136/bmj.g63 (Published 6 January 2014)
Cite this as: BMJ 2014;348:g63

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Can data fix the problem?

Restoring Invisible and Abandoned Trials

Bringing abandoned trials to light in a way that is transparent and accountable

Publish, or be published

Using data as a tool for corrective action

• Restorative authors

• Position: “If you won’t publish, we will.”

or correct, retract, and republish
RIAT process overview

Selection  **RIATAR** (Audit record: shows what’s in and what’s out and why)
- Report analyses per protocol
- Identify analyses which are NOT per protocol
- All available as web appendices

8000 page CSR

Restored publication  10 page journal article

(slide courtesy Tom Jefferson)
Clinical Study Reports in our possession

<table>
<thead>
<tr>
<th>Principles</th>
<th>Total number of CSRs</th>
<th>Trials Period</th>
<th>Total Pages</th>
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Amgen Epoetin Alfa study 930107
AstraZeneca quetiapine study 015, 041, 049, 135, 125, 127, 126
Bristol-Myers Squibb clopidogrel study CAPRIE, CURE, CLARITY, COMMIT, PICOLO
Bristol-Myers Squibb aripiprazole study CN138135
GSK H5N1 pandemic influenza vaccine studies H5N1-008, H5N1-011 EXT 008
GSK paroxetine study 329, 377, 453, 511, 701, 704, 715, 676, 716
GSK zanamivir study 167-101, 167T3-11, JNAI- 01, JNAI-04, JNAI-07, NAi30008, NAi30009, NAi30010, NAi30011, NAi30012, NAi30015, NAi30020, NAi30028, NAi30031, NAi30034, NAIA2005, NAIA2006, NAIA2010, NAIA3002, NAIA3003, NAIA3004, NAIA3005, NAIA4006, NAIA4007, NAIA4008, NAIA4009, NAIA4013, NAIA4014, PE-01
Merck rofecoxib study 078
Novartis Fluad studies V87P1, V87P6
Pfizer atorvastatin study 981080
Pfizer reboxetine study 9, 91, 8, 32a, 17, 15, 13, 16, 35, 49, 50, 45, 34, 47, 46, 52, 43, 32, 96, 71, 206,
Roche oseltamivir studies WV15673 WV15697, WV15670, WV15671, NP15757, WV15730, WV15708, WV15707, M76001, WV15799, WV15825, WV15758, WV15812 WV15872, WV15759 WV15871, WV15876 WV15819 WV15978, WP16263, WV16193, WV16871
Rowtasha arthonat study MA-CT-10-002
Takeda pioglitazone study PNFP-001
How to RIAT

1. Obtain clinical study reports and any other study data
2. Collect documentation of trial abandonment
3. Issue a “call to action” by publicly registering your possession of data sufficient for publication
4. Collect documentation of the need for restoration
5. Presubmission inquiry to RIAT friendly journal
6. Prepare and submit manuscript according to RIAT procedures

Summarized from Table 2, BMJ 2013;346:f2865.
Submit here

- Article
- Data
- Audit record

- BMJ
- PLOS Medicine
- Antivir Ther
- Cephalalgia
- Circulation
- Clinical Diabetes
- Diabetes
- Diabetes Care
- Diabetes Spectrum
- Headache
- J Affect Disord
- J Infect
- JAMA
- JAMA Internal Medicine
- Journal of the American Medical Directors Association (JAMDA)
- Lancet
- Pediatrics
- PLOS ONE
- Trials
- Journal of Negative Results in BioMedicine
9 RCTs of duloxetine

Re: Restoring invisible and abandoned trials: a call for people to publish the findings

21 June 2013

In response to the proposal by Doshi and colleagues for restoring invisible and abandoned trials (RIAT), we wish to register that we are in possession of data sufficient for publication of nine placebo controlled trials of duloxetine for the treatment of major depressive disorder (see attached table for further details). We believe that there are incomplete primary publications for seven of these trials, and no primary publications for two trials.

Clinical study report data held by NCC for 9 trials of duloxetine.pdf

Competing interests: None declared

Source: http://www.bmj.com/content/346/bmj.f2865?tab=responses
Current RIAT teams

Paroxetine study 329

On 15 July 2013, I signalled intent to work with a team of scientists to republish study 329 of paroxetine in children and adolescents, in accordance with the RIAT guidelines. Shortly afterwards GSK set up a process for researchers to ‘submit research proposals and request anonymised data from clinical studies’. Although they only included studies conducted since 2007, they offered the opportunity to ‘enquire about the availability of data from our clinical studies that are not listed on the site before they submit a research proposal’. I made such a query in relation to study 329 on 4 August. GSK’s website designates the status of my query as ‘under review’. It is not seem plausible that it would take 3 weeks to decide whether data is available.

In the absence of any apparent means to find anything more through the GSK website, I post this rapid response as an open letter to GSK seeking more information.

Competing interests: None declared

Source: http://www.bmj.com/content/346/bmj.f2865?tab=responses
"8-way" Bendectin Study

Re: Restoring invisible and abandoned trials: Bendectin trial

Following the publication of the Restoring invisible and abandoned trials (RIAT) paper [1], we notified 4 members of the Bendectin Peer Group on 8 August 2013 that we intend to publish the results of the unpublished 1970s study on the efficacy of doxylamine and pyridoxine ("8-way" Bendectin Study). As of 25 September 2013, 3 did not respond to our letter and 1 responded but did not register an intent to publish the trial. We are now publicly declaring our intention to publish the findings of this clinical trial.

Reference
2.

Competing interests: None declared

Source: http://www.bmj.com/content/346/bmj.f2865?tab=responses
Current RIAT teams

CEA Second-Look study

Re: Restoring invisible and abandoned trials: a call for people to publish the findings

27 October 2013

Dear BMJ Editors

In response to the proposal by Doshi and colleagues for restoring invisible and abandoned trials (RIAT) we wish to register that we have restored data sufficient for publication of the CEA Second-Look Trial of carcinoembryonic antigen prompted repeat surgery for colorectal cancer. We are ready to publish the results.

The trial was started in 1982 and was closed by the data monitoring committee in 1993 because it was highly unlikely that any survival advantage would be demonstrated after 1447 patients had been enrolled and 216 had been randomised. That decision was based on results presented to the British Oncological Association in 1994 and summarised in a letter to the Journal of the American Medical Association. Work on publishing the results of the trial came to a halt in 1994.

We looked for the CEA Second-Look Trial result because it was relevant to the

Source: http://www.bmj.com/content/346/bmj.f2865?tab=responses
Why journals?

CAPACITY AND KNOW-HOW
• Systematic reviewers search the literature
• Guideline writing committees, too
• Average physician won’t read more

CULTURE
• Peer-review, tenure and promotion

CONVENIENCE
• Everybody needs a summary sometimes
EBM decision making framework:
“Evidence”
+ clinician experience
+ patient values
Credible publications

RIAT aims to raise the bar on publishing trials
• Link journal length articles **with** data
• Provide an **audit trail** so decisions and responsibility are explicit

RIAT is a proposal for a new standard
• Journal articles without data instantly downgraded

RIAT articles contain three elements:
1. **article**
2. **data**
3. **audit**
Questions

- Away with publications?
- Taking credit for others work?
- Misleading analyses?
- Muddying the waters?
Thank you